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TITLE: Early Detection of Clinically Significant Prostate Cancer Using Ultrasonic Acoustic Radiation Force Impulse (ARFI) Imaging

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14. ABSTRACT
Prostate cancer (PCa) is the second most common cancer in men in the United States, with over 220,000 cases newly diagnosed, and over 27,000 deaths annually [1]. The current standard of care for prostate cancer diagnosis is to perform ultrasound guided biopsies is specific locations in the prostate, however, because prostate cancer does not have a unique appearance in ultrasound, these biopsies are not targeted to regions that look like cancer. As a result, these biopsy procedures can miss, leading to an incorrect diagnosis. Many men with prostate cancer have multiple separate biopsy procedures before finding it. Another problem is that cancer often occurs in multiple places in the prostate, and, the current biopsy approach does not necessarily find the most aggressive cancer in the prostate. We have preliminary data supporting the hypothesis that the 3D ARFI imaging biopsy targeting system we propose to develop will enable visualization of the most aggressive cancer in the prostate. Our system uses ultrasound to make pictures of how stiff tissues are and provides different information than normal ultrasound images. Therefore, the system will be low-cost, and can be easily incorporated into Urology clinics where biopsies are normally performed. If successful, our system will enable first time biopsy procedures to be targeted toward the most aggressive cancer in the prostate.

15. SUBJECT TERMS
Prostate Cancer Imaging, Image guided biopsy, Ultrasound elasticity imaging, ARFI imaging

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a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

Prostate cancer (PCa) is the second most common cancer in men in the United States, with over 220,000 cases newly diagnosed, and over 27,000 deaths annually. Screening methods are now widely used in the United States and Europe to detect PCa, including digital rectal examination (DRE), and prostate-specific antigen (PSA) analysis. Prostate biopsies are performed to diagnose PCa when suspicion is raised through these screening mechanisms. The clinical standard for performing prostate biopsy is ultrasound-guided, transrectal/transperineal, laterally-directed 18G needle cores, with 10-12 cores systematically sampling different regions of the prostate. Current ultrasonic prostate imaging does not facilitate targeting biopsies to suspicious regions because PCa does not have unique B-mode image characteristics that can delineate diseased from normal structures and benign pathologies. Therefore, the current standard of care has poor sensitivity, mainly because the sampling grid only randomly intersects the pathologic tissues. The purpose of our work is to develop a 3D ultrasound acoustic radiation force impulse (3D-ARFI) elasticity imaging system to facilitate targeting prostate biopsies toward regions that are suspicious for clinically significant cancer. The scope of the work includes three specific aims: 1) To develop and implement a clinic-ready 3D ARFI imaging system on a next-generation scanner with a dedicated ARFI power supply using custom sequences and automated probe rotation/positioning to interrogate the entire prostate gland, including the anterior region, with high resolution and realtime data processing. 2) To integrate ARFI & B-mode data in real-time with 3D Slicer and the Image-Guided Surgical Toolkit for rapid 3D visualization and image volume interpretation, followed by automated transducer positioning in a user-selected image plane for biopsy targeting of CSD, and to assess system performance in phantoms. 3) To evaluate the performance of the clinic-ready 3D ARFI prostate biopsy guidance system in vivo in humans for targeting clinically significant prostate disease.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Prostate Cancer, Elasticity Imaging, Ultrasound, Prostate biopsy, Image-guided biopsy, Acoustic Radiation Force Impulse (ARFI) imaging, 3D Slicer, 3D scan conversion and visualization, Clinically significant prostate cancer biopsy

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

Specific Aim 1: Develop 3D ARFI imaging prototype	Months	% complete
Major Task 1: 3D ARFI implementation		
Subtask 1: Develop sequencing tools on new scanner, explore multi-focal-zone configurations for range of prostate sizes	1-6	75%
Subtask 2: Zoom-mode ARFI single plane implementation	6-12	100%
Subtask 3: Perform acoustic output analysis on final sequences	14-16	25%
Subtask 4: Optimizing Feedback System for Rotation Stage	12-18	100%
Specific Aim 2: Integrate ARFI/B-mode imaging with 3D-Slicer/PLUS; perform phantom validation studies		
Major Task 2: Integration of ARFI with 3D-Slicer/PLUS		
Subtask 1: Real-time ARFI Image Generation and 3D Slicer Display	4-16	100%
Subtask 2: PLUS Biopsy Guidance Integration	8-18	100%
Major Task 3: Phantom Testing and Validation	Months	Investigator(s)
Subtask 1: Prostate volume and lesion localization validation	10-18	100%
Subtask 2: User selection of target location validation	12-18	100%
Subtask 3: Perform biopsy guided targeting in phantoms	14-18	75%
Specific Aim 3: Pilot clinical study		
Major Task 4: Assess performance of 3D ARFI biopsy system		
Subtask 1: Finalize protocol and obtain IRB approval	12-18	10%
Subtask 2: perform 3D-ARFI targeted biopsies in 30 patients expecting MR-US fusion guided biopsies	18-33	0%
Subtask 3: analyze data comparing biopsy results; publish results	33-36	0%

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

We are happy to report that we are on schedule with respect to our target goals. The individual aims and their major tasks and subtasks are reach repeated below with progress discussed as well as an indication of the percentage of completed effort following each sub-task.

Aim 1 of our project was: *To develop and implement a clinic-ready 3D ARFI imaging system on a next-generation scanner with a dedicated ARFI power supply using custom sequences and automated probe rotation/positioning to interrogate the entire prostate gland, including the anterior region, with high resolution*

and realtime data processing. This aim had 1 major task with four associated subtasks that have been achieved as described below.

Subtask 1: Develop sequencing tools on new scanner, explore multi-focal-zone configurations for range of prostate sizes (Months 1-6)

Our new scanner has two sequencing modes: a rapid prototyping mode that is used to iterate on sequencing approaches and, once finalized, a clinical implementation mode. We have successfully explored the use of multiple focal zone configurations using a custom designed transducer for these studies. *Figure 1* below portrays a 3D ARFI image volume obtained in a tissue mimicking prostate phantom using our optimized multi-focal-zone (5 zones) sequences on our new scanner, as well a comparison displacement profile with the older 3 focal zone system and original transducer. Although it would be possible to perform clinical scanning with this prototype mode, we now have the expertise in-house to integrate our sequences into the clinical implementation mode on this scanner, which we plan to do prior to performing the pilot clinical studies in aim 3.

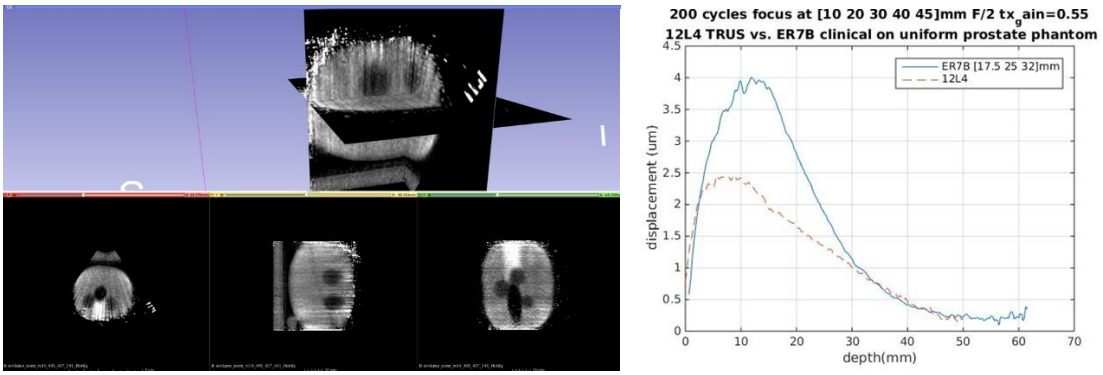

Figure 1 Left: 3D ARFI image volume of tissue mimicking prostate phantom portraying good signal quality throughout the entire gland, and portraying 3 high contrast stiff (dark) lesions. Images obtained using the rapid-prototyping sequencing mode on the scanner, using 5 focal zones per interrogation line, with a prototype custom designed TRUS transducer for ARFI imaging. Right: Comparison of prototype 12L4 displacement magnitude with earlier probe – although the displacement profile is more uniform across depth with the 12L4, the lower overall magnitudes at shallower depths are not ideal, and we continue to iterate on the sequencing to improve performance.

Status: 75% complete.

Subtask 2: Zoom mode ARFI single plane implementation (Months 6-12)

We have successfully implemented several single plane zoom mode sequences that maximize imaging contrast and resolution within a single imaging plane.

Status: Completed.

Subtask 3: Perform acoustic output analysis on final sequences (Months 14-16)

We have performed initial thermal characterization of the probe heating obtained with our custom transducer/system. However, we will repeat output characterization once we implement our sequences within the clinical implementation mode prior to performing the studies in aim 3.

Status: 25% complete.

Subtask 4: Optimizing Feedback System for Rotation Stage (Months 12-18)

We have successfully upgraded our rotation stage to operate with the new scanner, including providing both positional control signals and feedback on positional accuracy. As described below, we have also integrated non-uniform positional feedback capabilities into our 3D visualization tools as shown in *Figure 2*.

Status: Completed.

Aim 2 of the project was: *To integrate ARFI and B-mode data in real-time with 3D slicer and the Image-Guided Surgical Toolkit (IGSTK) to enable rapid 3D visualization and image volume interpretation followed by automated transducer positioning in the user-selected image plane for biopsy targeting of CSD, and to assess system performance in phantom studies.* This aim was broken down into two major tasks with associated subtasks that have been achieved as described below.

Major Task: Integration of ARFI with 3D Slicer / IGSTK

Subtask: Real-time ARFI Image Generation and 3D Slicer Display (Months 4-16)

Working with Siemens engineers, we have integrated real-time ARFI image processing tools that directly access raw IQ data in the scanner memory to generate ARFI displacement maps at a user-specified time step after our acoustic radiation force excitation. These processing tools have been written in C# to run in a multithreaded CPU infrastructure on the ultrasound scanner, rendering image data in < 1 second. These image data are written to a local disk / memory, where they can be natively read into the 3D Slicer environment via a custom Python module (https://github.com/mlp6/SlicerITKUltrasound). This module can leverage both VTK and ITK (https://github.com/KitwareMedical/ITKUltrasound) 3D interpolation libraries to render 3D ARFI image volumes in 0.2-5 seconds, dependent on the spatial resolution and order of the spatial interpolant.

Status: Completed.

Subtask: IGSTK Biopsy Guidance Integration (Months 8-18)

Originally the IGSTK was going to be used for its 3D positioning tools to integrate our 3D rotation motor with our 3D data visualization. Given the strong performance of the volumetric display natively achieved using 3D Slicer, we were able to avoid integration into another piece of software, and instead have written a custom Python GUI to perform both:

1. Automated 3D ARFI/B-mode image acquisition over a user-specified range of angles and angular increment, and
2. The ability to place fiducial markers at suspicious regions in the 3D ARFI/B-mode imaging volumes and return spatial coordinates to allow the clinician to return to that location to perform additional imaging ("zoom mode"), and subsequent image-guided biopsy.

Figure 2 shows a screenshot of the existing GUI, as it can be run natively on the Siemens ultrasound scanner. This GUI is written in Python and shares a directly data-passing infrastructure with 3D slicer to seamlessly integrate imaging position in 3D space with the rendered ARFI/B-mode imaging volumes.

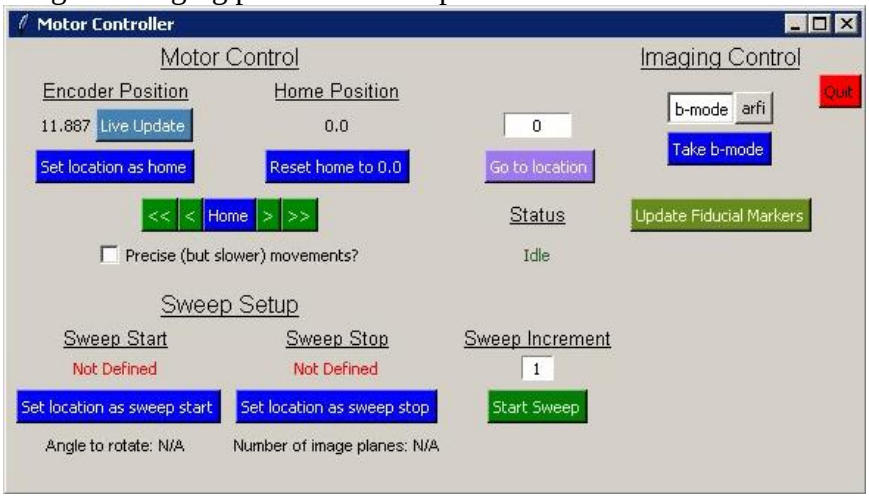

Figure 2: Screenshot of 10he GUI that has been written to run on the ultrasound scanner and seamlessly communicate with 3D Slicer to generate 3D ARFI/B-mode imaging volumes to identify regions suspicious for targeted biopsy.

Status: Completed.

Major Task: Phantom Testing and Validation

Subtask: Prostate volume and lesion localization validation (Months 10-18)

Using the 3D Slicer visualization and positioning tools developed in the first major task, we have tested the performance of these tools using existing prostate data from previous studies and phantom studies. *Figure 3* shows an example of the 3D volumetric data rendering and fiducial marker spatial localization of a lesion to be targeted for biopsy using previously-acquired *in vivo* prostate data. The time to generate the displacements from raw IQ data was < 1 second, and the time to render the 3D ARFI imaging volume was also < 1 second using 0.3 mm voxel sampling.

One source of error in our earlier implementation of 3D ARFI imaging was an assumed uniform angular spacing between raw 2D image acquisition planes, which was done to accelerate the 3D rendering of the data. Using our newly optimized tools from the first major task of this aim, we are now able to use the actual angular spacing of our datasets to achieve a more accurate representation of our prostate and associate lesion volumes. *Figure 4* shows data on our accuracy to localize wire targets in a calibrated phantom using the older method of assumed uniform angular position.

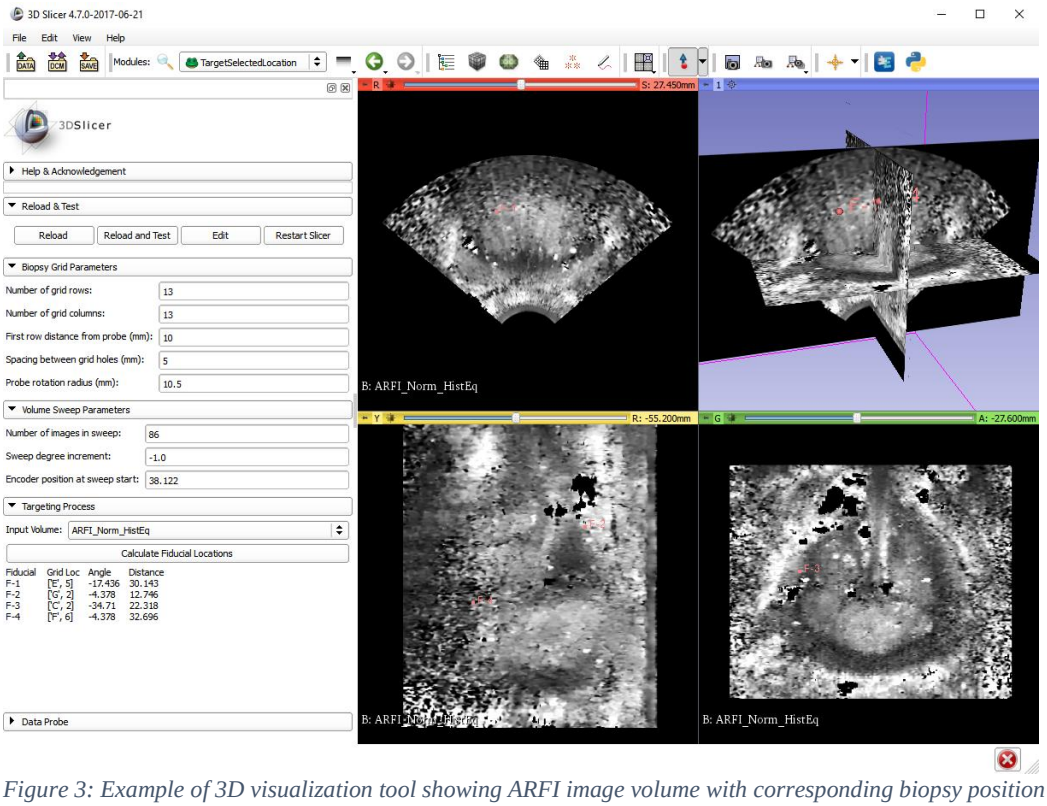

Figure 3: Example of 3D visualization tool showing ARFI image volume with corresponding biopsy position data being rendered in real-time in the lower left panel based on the clinician's choice of fiducial markers in the 3D image dataset.

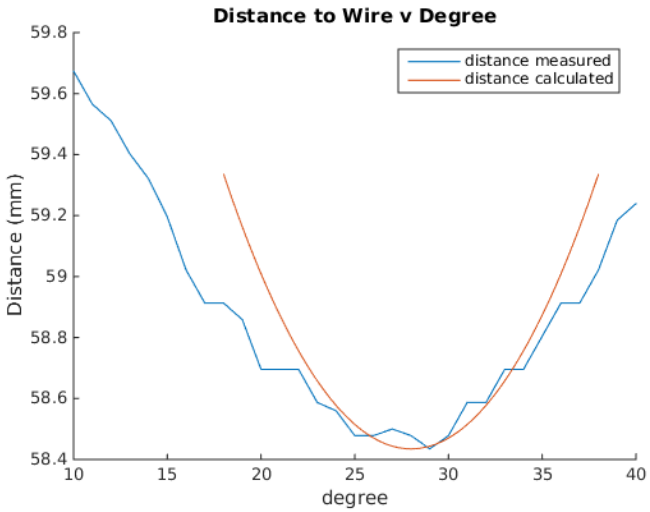

Figure 4: Accuracy of measured position versus expected position using the original position-determination algorithm.

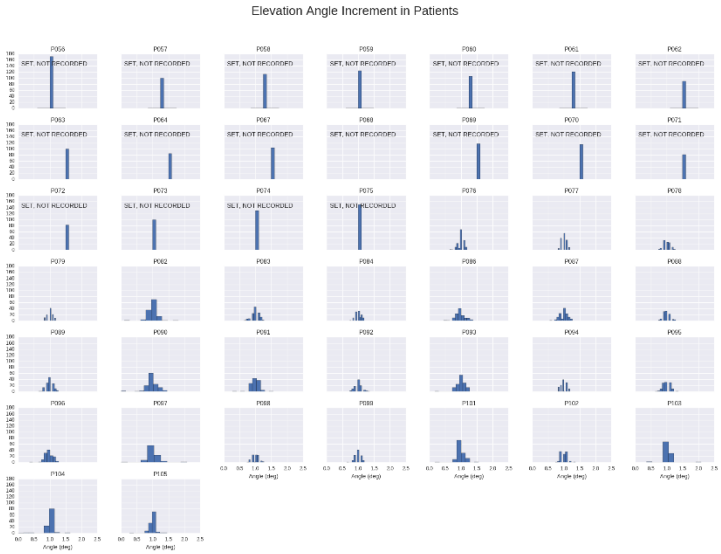

Figure 5: Histograms of the improvements in angular accuracy obtained when using the actual rotational positions instead of the assumed, uniform positions for previously-acquired study subject data. Note that in subjects ≤P075, we did not have the capability to acquire the actual positions, while in ≥P076, we have that more accurate position data. Our latest visualization tools developed under this funding have now accelerated our 3D volume rendering to allow us to use non-uniform angular spacing in our data visualization interface, leading to significantly improved spatial accuracy and ultimately more accurate lesion volume and position data.

Status: Completed.

Subtask: User selection of target location validation (Months 12-18)

As described under the second subtask in the first major task for this aim, we have written a custom GUI (*Figure 2*) that integrates with our 3D Slicer visualization tools that allows the user to:

1. Place fiducial markers in regions of suspicion throughout the 3D imaging dataset, as guided by both ARFI and B-mode images,
2. Automatically receive information about the 3D position of those lesions based on the placement of the fiducial marker, and
3. Have the flexibility to choose to move the imaging probe to directly image ("zoom mode") and image-guide a biopsy towards a targeted lesion(s).

Status: Completed.

Subtask: Perform biopsy guided targeting in phantoms (Months 14-18)

We have performed a controlled phantom study to assess the accuracy of our new biopsy visualization and guidance tools. Three locations 30 mm from the face of the transducer at various angles from its origin position were chosen for this phantom analysis. For each location, the 3D Slicer module computed the orientation necessary for the ultrasound probe, and the motor controller moved the probe to that location. A biopsy needle was inserted at each location. With the needle in place, the angle and distance between the calculated and actual locations were used to quantify the offset in positioning.

Table 1: Absolute needle tip offset from fiducial marker location as a function of angle position (center of image volume at 0) for a 30 mm target depth.

Angle Position (degrees)	Mean Absolute Needle Tip Offset (mm)
0	0.03
32	1.4
44	2

Given the size of our targeted lesions of suspicion, needle tips within 2 mm of target location are considered acceptable to ensure that samples are target tissue are acquired in the biopsy sample.

This procedure of biopsy guidance performance will be used throughout the remaining studies to confirm calibration of our imaging / positioning system.

Status: 75% complete.

Aim 3 of our project was: *To evaluate the performance of the clinic-ready 3D ARFI prostate biopsy guidance system in vivo in humans for targeting clinically significant prostate disease.*

This aim had 1 major task with three associated subtasks, the last two of which include obtaining and analyzing clinical data with the 3D ARFI system, neither of which have been initiated as they are proposed to begin in month 18 of funding. The first subtask involves finalizing an IRB protocol and obtaining approval for our proposed studies. We are currently working with our clinical collaborator (Dr. Polascik) to determine the optimal patient population in which to demonstrate our system in the coming year. Since the original submission, Duke has greatly reduced the number of transperineal side-fire biopsies (i.e. saturation biopsies) performed at the medical center which had been our envisioned patient population. We are discussing several alternative patient groups and protocols for evaluation of the 3D ARFI system and visualization tools developed herein, with the most likely being clinical data acquisition prior to surgery in patients receiving radical prostatectomy and subsequent correlation through image registration between pre-operative multi-parametric 3D MRI images and 3D ARFI images to compare targeting performance between the two imaging modalities.

Status: IRB planning initiated. (10% complete)

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater

proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Our work in this first year of funding has been dedicated to technical development and implementation. We have provided two 3D visualization tools to the 3D Slicer community working group which are freely available for download. (https://github.com/mlp6/SlicerITKUltrasound and https://github.com/KitwareMedical/ITKUltrasound) These include our rapid 3D scan-conversion tool, and our semi-automated image segmentation tool.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We propose to perform the tasks that have not yet been completed as described for year 2 of funding in the original SOW, which include:

Aim 1, subtask 1: extend the optimal multi-focal zone sequences from the rapid-prototype implementation to the imaging software on our scanner
Aim1, subtask 3: perform acoustic output characterization on our final sequences prior to performing imaging in the clinic.
Aim 2, subtask 3: phantom validation – we will employ our validated targeting protocols using the final sequences/clinical implementation of the 3D ARFI imaging tool in phantoms to ensure performance comparable or better to what we have achieved with the rapid-prototype system.
Aim 3, subtask 1: IRB - we will obtain IRB approval for studies enabling validation of our 3D ARFI biopsy targeting system.
Aim 3, subtask 2: *In vivo* studies - We will initiate *in vivo* studies, initially to obtain pilot data to verify system operation, and, once validated, to begin accrual of data enabling comparison of targeting performance with mp-MRI data.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

We propose to design and build a 3D ARFI ultrasound clinic-ready prostate biopsy guidance system that will enable screening the entire prostate volume for regions suspicious for clinically significant prostate disease (CSD), followed by real-time ultrasonic guidance during first-time targeted needle biopsy of these regions. If, as we hypothesize, this system has the same or better yield for positive biopsy cores for CSD as that obtained with MR-US fusion based targeted prostate biopsy methods, this system has the potential to change the standard of care for prostate cancer diagnosis by enabling detection of the most significant disease present in the prostate upon initial diagnosis, facilitating improved treatment decisions and patient outcomes. Because the proposed system is ultrasonically based, it can be readily integrated with commercial ultrasound scanners, which will enable rapid translation and integration into the current clinical work flow. The additional time required to identify regions suspicious for cancer in the prostate, which could approximately double what is currently required for systematic sampling (30 minutes vs. 15 minutes), will be well warranted given the anticipated improvement in diagnostic outcomes. The ability to make initial treatment decisions based upon first-time biopsy results from the most significant disease present in the gland would lead to a much needed paradigm shift in prostate cancer diagnosis and treatment, significantly reducing the over-treatment and under-diagnosis problems that plague current practice.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

The 3D visualization tools that we have developed using the 3D Slicer toolset can be utilized for any image fusion technologies that employ ultrasound.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Ultimately, successful completion of this project will improve the quality of life for men with suspicion of prostate cancer, as it will enable accurate diagnosis of the most significant cancer present in the gland upon first-time biopsy, facilitating appropriate treatment decisions.

5. CHANGES/PROBLEMS: The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

While we remain on schedule to initiate imaging studies this spring, due to the decrease in the number of transperineal biopsies performed by Dr. Polasick and the award of another grant (an NIH R01 industrial partnership grant) which will develop a custom transducer/biopsy needle guide that will enable side-fire, transrectal biopsy with an ARFI capable transducer, as opposed to a transperineal biopsy, we are now planning for the clinical studies in aim 3 of this work to employ correlation between the regions identified for biopsy targeting during 3D ARFI imaging performed pre-operatively with registered multi-parametric MR imaging serving as the gold standard in patients receiving radical prostatectomy.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Nothing to report.

Changes that had a significant impact on expenditures
Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals.

Not Applicable.

Significant changes in use of biohazards and/or select agents

Not Applicable.

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

1. Palmeri M, Nightingale K. "Chapter 17: Acoustic Radiation Force Impulse Imaging for Targeting: Correlation with Histology", In: Polascik T, editor, Imaging and Focal Therapy of Early Prostate Cancer, Current Clinical Urology, 2nd edition, Springer, 2017.

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

We have provided two 3D visualization tools to the 3D Slicer community working group which are freely available for download that were developed with funding from this award: https://github.com/mlp6/SlicerITKUltrasound and https://github.com/KitwareMedical/ITKUltrasound. These include our rapid 3D scan-conversion tool, as well as our semi-automated image segmentation tool.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number.

Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**

  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS-Amberly completing

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name: Kathryn Nightingale, Ph.D.
Project Roll: PI
Nearest person month worked: 0.7 academic months; 1 summer month
Contribution to Project: Dr. Nightingale directs all aspects of the proposed work. She advises the graduate students in the implementation of the required system sequencing and real-time processing algorithms; coordinates communication between team members during all project phases; and interfaces with Siemens during tool development and implementation on the prototype scanner.
Funding Support: This award

Name: Mark Palmeri, M.D., Ph.D.
Project Roll: Co-Investigator

Nearest person month worked: 2 summer months
Contribution to Project: Dr. Palmeri oversaw and contributed to the real-time implementation of 3D volume rendering accomplished in Aim 2.
Funding Support: This award

Name: Thomas Polascik, M.D
Project Roll: Co-Investigator
Nearest person month worked: 0.5 summer months
Contribution to Project: Dr. Polascik is a Professor in the Department of Urology in the Duke University Medical Center. He provides feedback on the 3D visualization tools and clinical study design, and is going to identify patients for recruitment, and perform the proposed in vivo ARFI imaging.
Funding Support: This award

Name: Adam Pely
Project Roll: Graduate Research Assistant
Nearest person month worked: 4 calendar months
Contribution to Project: Implemented the technical aspects of the proposed studies on the scanner, specifically the multi-focal zone and rapid prototype sequencing tools.
Funding Support: This award; Training in Medical Imaging NIH - 5T32EB001040

Name: Derek Chan
Project Roll: Graduate Research Assistant
Nearest person month worked: 1.6 calendar months
Contribution to Project: Implemented the technical aspects of the proposed studies, specifically working on new data processing algorithms.
Funding Support: This award

Name: Matthew Huber
Project Roll: Research Assistant
Nearest person month worked: 3 calendar months
Contribution to Project: Implemented the technical aspects of the proposed studies on the scanner, specifically developing the rotation stage GUI with feedback controls and positional information, and performing the phantom validation studies.
Funding Support: This award

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

The following grants have ended:

Title: Acoustic Radiation Force Based Hepatic Elasticity Quantification and Imaging
Sponsor: NIH - 5R01EB002132 (Nightingale)
Grants Management Specialist: James E. Huff
Email: huffj@mail.nih.gov
Phone: 301-451-4786
Period Performance: 8/5/12-7/31/16
Goals: The goal of this project is to improve the precision of hepatic stiffness quantification methods through the use of 3D volumetric imaging, in addition to developing high spatial resolution quantitative radiation force based stiffness imaging methods.
Aims: 1. To develop and implement novel stiffness reconstruction methods combining qualitative and quantitative ARFI technologies to provide structurally accurate quantitative stiffness estimates and images of hepatic tumors.; 2. To develop and implement 3D shear wave speed monitoring beam sequences and algorithms using a 2D matrix array to improve the accuracy and precision of shear wave speed estimates.
3. To evaluate this next-generation system in the context of hepatic fibrosis staging and hepatic tumor characterization.

Title: Radiation Force Imaging of Prostate Cancer and Guidance of Biopsy Procedures
Supporting Agency: NIH, 5R01-CA-142824-05 (Nightingale)
Funding Agency Grants Officer: Rosemary Ward, 240-276-6320, wardros@mail.nih.gov
Performance Period: 1/18/10-12/31/15
Project Goals: The overall goal of the proposed work is to develop a non-invasive, real-time, in vivo radiation force based elasticity imaging system capable of visualizing and differentiating structures and regions of pathology within the prostate.
Specific Aims: 1. To design and optimize ARFI prostate imaging sequences and to implement them on a 64:1 parallel receive beam system. 2. To develop shear stiffness quantification algorithms with spatial resolution approaching 1 mm2, and to design and implement pulse sequences capable of combined ARFI imaging and quantitative shear modulus estimates from a single excitation. 3. To correlate in vivo and ex vivo ARFI/shear modulus findings with tissue histology (e.g., normal structure, PCa, BPH, inflammation), and to correlate local PCa Gleason pattern with ARFI/shear modulus suspicion level.

Title: A Pilot Study in Human Subjects Evaluating the Use of the NanoKnife System for Ablation of Prostate Cancer Tissue in a Low Risk Patient Population
Supporting Agency: AngioDynamics, ON-NK310 (Polascik)
Funding Agency Grants Officer: Unknown
Performance Period: 1/1/14-11/30/15
Project Goals: 1. To determine the NanoKnife treatment procedural and short-term posttreatment safety profile by evaluating adverse event incidence, type, duration, severity and relationship to study device.
2. Determine the NanoKnife treatment morbidity profile by evaluating urinary and erectile function.
Specific Aims: N/A

Sponsor: Kitware, Inc. (Polascik)
Period Funding: 04/01/15-03/31/16
Title: Prostate Cancer Assessment and Treatment Guidance via Integrated 3D ARFI Elasticity Imaging and Multi-Parametric MRI
Goals/Aims: Evaluate if combined Shear Wave Elasticity (SWE) imaging and multi-parametric magnetic resonance imaging (mpMRI) will enable sensitive and specific detection of PCA and provide accurate delineation of PCA margins.
Vicki Rafferty (518) 881-4401
contracts@kitware.com

Sponsor: Radiological Society of North America
Award number: HHSN268201300071C (Palmeri)
Period Funding: 9/30/14-9/29/15
Title: Development & Validation of Simulations and Phantoms Mimicking the Viscoelastic Properties of Human Liver
Goals/Aims: Generate simulated shear wave datasets in elastic and viscoelastic media to match tissue-mimicking phantom and human liver datasets for shear wave speed estimation algorithm validation and development.
Vincent Vitale (630)481-1008
vvitale@rsna.org

The following new grants have been funded:

Title: Image guided targeted biopsy of clinically significant prostate cancer with acoustic radiation force
Effort: 1 Academic and 1 Summer (25%) (Nightingale)
Sponsor: NIH-2R01CA142824-06A1
Period of Performance: 8/1/17-7/31/22
Grants Management Specialist: Romy Reis
Email: mondesir@mail.nih.gov
Phone: 204-276-6316
Level of Funding: $2,529,312
Goals/Aims: Partnership with industry (Siemens) to fabricate a custom designed transrectal, side-fire array transducer and biopsy guide with needle trajectory capability throughout the prostate in order to enable in-clinic 3D screening and targeted prostate biopsy. 1) To translate our prototype system into a clinic-ready system through: development and integration of a custom designed, side-fire transrectal transducer and biopsy needle guides, implementation of our data processing and 3D data visualization tools on-board a state-of-the-art prototype ultrasound scanner, and integration of a motorized rotation system for automated targeted biopsy image plane positioning. 2) To assess the performance of the 3D TRUS ARFI targeted biopsy guidance system in tissue mimicking phantoms. 3) To assess the performance of 3D ARFI screening and targeted biopsy guidance in vivo in humans in targeting clinically significant prostate disease.

Title: Improved Ultrasound Imaging Using Elevated Acoustic Output
Effort: 0.75 Academic and 1.5 Summer (equivalent to 18.8% calendar effort) (Nightingale)
Sponsor: NIH 1R01EB022106
Grants Management Specialist: Angela Eldridge
Email: ae49k@nih.gov
Phone: 301-451-4793
Period of Performance: 3/1/16-12/31/19
Level of funding: $1,776,644
Goals: The primary goals of this work are to optimize harmonic image quality using acoustic output levels that exceed those currently employed by commercial systems, and to quantify the resulting image quality improvements in the context of abdominal imaging.
Aims: 1) To extend our 3D nonlinear simulation tools to perform a parametric analysis of varying tissue properties and transducer configurations to optimize harmonic signal generation and image quality in elevated MI pulse inversion har-monic imaging, and to determine the relationship between water-based estimates and in situ measurements in the elevated MI output regime. 2) To design and implement a real-time prototype elevated MI system using commercial curvilinear abdominal arrays and a custom designed prototype large aperture low frequency diagnostic array on a commercial grade scanner. 3) To quantify improvements in imaging performance afforded by the use of elevated MIs in patients scheduled for ultrasonic abdominal imaging

studies, and in patients known to have malignant liver masses.

Title: Early Detection of Clinically Significant Prostate Cancer using Ultrasonic Acoustic Radiation Force Impulse (ARFI) Imaging
Time Commitment: 0.85 Academic/1 Summer (equivalent to 15.4% calendar effort)* (Nightingale)
Supporting Agency: United Stated Army Medical Research Acquisition Activity
Funding Agency Grants Officer: Kimberly Carter, kimberly.m.carter47.civ@mail.mil, (301) 619-2249.
Performance Period: 9/15/16-9/14/19
Level of Funding: $577,455
Project Goals: Our goal is to improve the diagnostic utility of ultrasonic prostate biopsy procedures by developing a biopsy guidance imaging system that is specific for CSD in the prostate.
Specific Aims:
1) To develop and implement a clinic-ready 3D ARFI imaging system on a prototype ultrasound scanner with a dedicated ARFI power supply using custom sequences and automated probe rotation/positioning to interrogate the entire prostate gland (including the anterior region) at high resolution with real-time data processing.
2) To integrate ARFI and B-mode data in real-time with 3D slicer and the Image-Guided Surgical Toolkit (IGSTK) to enable rapid 3D visualization and image volume interpretation followed by automated transducer positioning in the user-selected image plane for biopsy targeting of CSD, and to assess system performance in phantom studies.
3) To evaluate the performance of the clinic-ready 3D ARFI prostate biopsy guidance system in vivo in humans for targeting clinically significant prostate disease.

Title: Prospective registry to optimize critical care (DUCIMAS)
Time Commitment: 0.12 calendar months (Polascik)
Supporting Agency: Myriad Genetics, Inc.
Funding Agency Grants Officer: Unknown
Performance Period: 9/1/16-8/31/19
Level of Funding: $150,150
Project Goals: To address the problems associated with over-diagnosis and over-treatment of prostate cancer, we have developed the Duke Cancer Institute Multidisciplinary Active Surveillance (DUCIMAS) cohort. For those patients who wish to be screened for and are diagnosed with prostate cancer, this clinical pathway aims to provide the patient an up-to- date prostate cancer risk assessment. We plan to initiate a modem Active Surveillance protocol incorporating state-of-the-art multi-parametric MRI, MRI-fusion targeted prostate biopsy and molecular tissue RNA cell-cycle biomarkers (Prolaris) to better predict the risk of prostate cancer progression to improve risk stratification of patients to surveillance or intervention. This study provides the unique opportunity to assess the utility of mpMRI and Prolaris in Active Surveillance of an American cohort, with a high proportion of African American men.
Specific Aims: N/A

Title: A Phase 3 Study to Evaluate the Safety and Efficacy of Tc-MIP-1404 SPECT/CT Imaging to Detect Clinically Significant Prostate Cancer in Men with Biopsy Proven Low-Grade Prostate Cancer who are Candidates for Active Surveillance (proSPECT-AS)
Time Commitment: 0.12 calendar months (Polascik)
Supporting Agency: Molecular Insight Pharmaceuticals, Inc.
Funding Agency Grants Officer: Unknown
Performance Period: 7/1/16-6/30/18
Level of Funding: based on enrollment/visits
Project Goals: This study will evaluate the sensitivity and specificity of 99mTc-MIP-1404 SPECT/CT image assessments to correctly identify subjects with previously unknown clinically significant prostate cancer.
Specific Aims: N/A

Sponsor: Gates Foundation
Award Number: OPP1142958 (Deshusses)
Level Funding: $341,337
Period of Funding: 11/11/15-1/31/17
Effort: .35 summer (Palmeri)
Title: The Anaerobic Digestion Pasteurization Latrine (ADPL)
Goals/Aims: To further the development of an Anaerobic Digestion Pasteurization Latrine (ADPL), a simple, energy neutral self-contained sanitation technology relying on anaerobic digestion and pasteurization of the treated effluent. This project will actively maintain and monitor five existing ADPL systems located in Kenya, India and the Philippines to provide solid evidence of treatment efficacy in the field for implementation in developing world poverty situations.
Grant Manager: Mary Heinlein, Coordinator, Grants and Contracts Management, (206) 726-7155, mary.heinlein@qatesfoundation.org

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

Nothing to report.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

Nothing to report.